

REMARKS

Claims 1-54 were pending in the instant application. Claims 16-54 have been withdrawn from consideration by the Examiner as indicated in the July 22, 2002 Office Action. Claims 1-15 have been canceled by this Amendment. New claims 55-64 have been presented. Support for the new claims can be found in the specification and in the claims as originally filed. Specifically, support can be found, *inter alia*, for claims 55-59 and 64, in the specification at page 9, line 20 to page 15, line 23, in Figures 1-4, and in original claim 9. Support can be found, *inter alia*, for claims 60-62 in original claims 1-8 and in Figures 1-4. Support for claim 63 can be found, *inter alia*, at page 16, lines 5-10. None of the newly added claims introduces any new matter. Accordingly, their entry is requested. Upon entry of the present Amendment, claims 55-64 will be pending and under examination.

In the July 22, 2002 Office Action, the Examiner acknowledged the Applicant's election with traverse of Group I and the single gene ADOA2A. However, the Examiner indicated that although she did not withdraw the Restriction Requirement, each of the genes recited in the claims was searched.

Examiner's Rejection Under 35 U.S.C. §112, first paragraph -
Enablement

The Examiner rejected claims 1-15 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, the Examiner stated that it was unclear how the data should be interpreted in that genes appeared in the Figures to

be both significant and insignificant. The Examiner particularly noted apparent confusion between Figure 3 and Figure 1. The Examiner further sought clarification with respect to which genes were referred to in Figure 2. The Examiner also noted that the art appears to reflect association between certain polymorphisms and ADHD in some populations but not in others.

The Examiner further stated that the claims directed to determining risk of ADHD were not enabled for all non-wild type alleles, asserting that the specification does not disclose a representative number of polymorphisms from the recited genes.

The Examiner moreover indicated that claim 9 is not enabled, asserting that it is directed to a "research project" in which one would need to do all necessary work to carry out a useful method.

Finally, the Examiner rejected claims 10-15, directed to determining a treatment modality for ADHD based upon detecting non-wild-type alleles, asserting that there is no guidance indicating what treatment would be suitable for what allele.

In response, Applicant respectfully traverses the Examiner's rejections under 35 U.S.C. § 112, first paragraph. To advance prosecution of the instant application, Applicant has canceled claims 1-15 and presented new claims 55-64, which Applicant asserts are fully enabled by the specification. With respect to the Examiner's contention that there is apparent confusion between the Figures and in the art, leading to an inability to interpret the data, Applicant respectfully disagrees. In that regard, Applicant emphasizes that the polygenic disorders disclosed in the present application, by nature, require analysis of multiple genes. As described in the specification, polygenic disorders are a unique group of disorders that are very different from single gene disorders. Unlike single gene disorders, genes contributing to a polygenic disorder may or may not show significant correlation when

analyzed individually by methods previously known in the art. However, when the methods of the present invention are employed to analyze genes in the context of other co-present genes, a determination can then be made as to whether any individual gene does in fact play a significant role in the polygenic disorder. Therefore, while some individual genes appear not to be significantly associated with ADHD based only on the data presented in Figure 1 (which involved individually selected and analyzed genes), Figure 3 presents data showing which genes are in fact significant as determined by the methods of the instant application (multivariate regression analysis by association of the candidate genes). Thus, Figure 1 identifies individual candidate genes selected from the literature, optimized by ANOVA, or developed independently in the inventor's laboratory (see specification, page 10), and their seeming significance, while Figure 3 identifies which genes are in fact significant as determined by the unique analysis methods of the present invention. Thus, for the multivariate regression analysis utilized in the claimed invention, all gene scores (from Figure 1) were added together and the non-significant ones were removed by backward elimination, based on the removal criteria described at page 11, lines 25-28 of the specification.

Moreover, Applicant points out that polygenic disorders are characterized by a great deal of genetic heterogeneity. Thus, for example, in one group of subjects with ADHD, the additive effect of hypothetical genes A, B, C, D, E, F, G, and H may be involved while genes I, J, K, and L are not significant. In contrast, in a second group with ADHD, the additive effects of genes A, C, F, G, H, I, J, K, and L may be significant, with genes B, D, and E being non-significant. If all the genes are reasonable candidates, they would be properly included in the group of candidate genes so that

the test of the additive effect of all genes will apply for all groups of subjects. Previously known methods have failed to make accommodation for the additive effect of multiple genes and for genetic heterogeneity, thereby resulting in a lack of progress in the art in understanding the genetics of polygenic disorders such as ADHD. P-values from methods which analyze one gene at a time, therefore, have little relevance to whether a gene in fact contributes to a polygenic disorder or trait. Accordingly, as described in the specification, the present invention uniquely analyzes multiple genes in multigene disorders, includes numerous genes in the analysis, and employs multivariate regression analysis to determine the total variance (r^2) of genes in different functional groups of genes. The present invention has led to the finding that different sets of functional genes are involved in different disorders. Specifically, for example, norepinephrine genes are preferentially involved in ADHD.

With respect to the Examiner's inquiry regarding the data presented in Figure 2, Applicant points out that the numbers of genes referred to for each disorder are those that are individually identified in Figure 3.

In light of the above, it should be apparent that the data presented in the present application are not, in fact, inconsistent. Therefore, it also should be apparent that the Examiner's concerns with respect to teachings in the art are no longer applicable. For example, The Tang reference, to which the Examiner referred, analyzed only one polymorphism in an attempt to correlate its significance with ADHD. The Tang reference itself, at page 487, final paragraph, acknowledges the limitation of this approach in determining whether the particular cited polymorphism does in fact play a significant role in ADHD. The present invention's additive approach overcomes this limitation.

With respect to the Examiner's assertion that the claims are not enabled for determining risk of ADHD by detecting a non-wild-type allele on the genes presented, Applicant has canceled claims 1-8 and presented new claims 60-62, and 64. Claims 60-62 are directed to methods of determining risk of ADHD based on detecting at least one of the recited non-wild-type alleles, and claim 64 is directed to determining risk based on detection of a non-wild-type allele of a gene determined by the claimed methods to contribute to ADHD. Applicant asserts that presentation of these new claims obviates this ground of the Examiner's rejection.

Applicant has also canceled claim 9 in favor of new claims 55-59, directed to methods of determining whether a gene contributes to ADHD.

Finally, Applicant has canceled claims 10-15, directed to methods of determining a treatment modality, in favor of new claim 63, directed to a method of treatment itself.

In view of the above remarks, and the presentation of new claims 55-64, Applicant asserts that all claims are fully enabled. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejections under 35 U.S.C. § 112, first paragraph.

Examiner's Rejection Under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 1-15 under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicant asserts that the cancellation of claims 1-15 and the presentation of new claims 55-64 obviates this rejection. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 112, second paragraph.

In view of the above remarks and presentation of new claims, it is believed that the present application is in condition for

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allowance. Reconsideration of the application and early notice of allowance are requested. The Examiner is invited to telephone the undersigned if it is deemed to expedite allowance.

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